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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/808,846	03/24/2004	Erwin Gelfand	2879-68-1	6711

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EXAMINER	
ROONEY, NORA MAUREEN	
ART UNIT	PAPER NUMBER
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/808,846	GELFAND ET AL.	
	Examiner	Art Unit	
	Nora M. Rooney	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 February 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *36-45* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *36-45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *24 March 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/06/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 36-53 are pending.

2. Applicant's election without traverse of the species asthma in the reply filed on 02/08/2007 is acknowledged.

3. Claims 36-53 are currently under examination as they read on a method for reducing airway hyperresponsiveness by administering a phosphoantigen to a mammal.

4. Applicant's IDS filed on 12/06/2004 is acknowledged.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 36-53 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. *This is a New Matter rejection for the following reasons*:

The method to reduce airway hyperresponsiveness in a mammal, comprising increasing gamma delta T cell action in a mammal that has, or is at risk of developing, a respiratory condition associated with airway hyperresponsiveness by administering a phosphoantigen to said mammal, wherein administration of said phosphoantigen reduces airway hyperresponsiveness in said mammal of claim 36; wherein the phosphoantigen comprises isoprenylpyrophosphate (IPP) of claim 37; wherein said pyrophosphate is administered so that gamma delta T cells in the lung tissue of said mammal increases of claim 38; wherein said phosphoantigen is administered so that gamma delta T cells in said mammal are activated of claim 39; wherein said phosphoantigen is targeted to gamma delta T cells in the lung tissue of said mammal of claim 40; wherein said phosphoantigen is targeted to gamma delta T cells having T cell receptor selected from the group consisting of a murine TCR comprising Vgamma4 and a human TCR comprising Vgamma1 of claim 41; wherein said phosphoantigen is administered by a route selected from the group consisting of inhaled, intratracheal and nasal routes of claim 42; wherein said phosphoantigen is administered to said mammal in an amount effecting to reduce airway hyperresponsiveness in said mammal as compared to prior to administration of said phosphoantigen of claim 43; wherein said phosphoantigen is administered with a pharmaceutically acceptable excipient of claim 44; wherein said phosphoantigen is administered within between 1 hour and 6 days of an initial diagnosis of airway hyperresponsiveness in said mammal of claim 45; wherein said phosphoantigen is administered within less than about 72 hours of an initial diagnosis of airway hyperresponsiveness in said mammal of claim 46; wherein said phosphoantigen is administered prior to development of airway hyperresponsiveness in said mammal; wherein increasing gamma delta T cell action by administration of said phosphoantigen decreases airway methacholine

responsiveness in said mammal of claim 48; wherein increasing gamma delta T cell action by administration of said phosphoantigen reduces airway hyperresponsiveness of said mammal such that the FEV1 value of said mammal is improved by at least about 5% of claim 49; wherein increasing gamma delta T cell action by administration of said phosphoantigen improves said mammal's $PC_{20methacholine}$ FEVt value obtained before increasing gamma delta T cell action when the mammal is provoked with a first concentration of methacholine is substantially the same as the $PC_{20methacholine}$ FEVt value obtained after increasing gamma delta T cell action when the mammal is provoked with double the amount of the first concentration of methacholine of claim 50; wherein said first concentration of methacholine is between about 0.01 mg/ml and about 8 mg/ml; wherein said airway hyperresponsiveness is associated with a disease selected from the group consisting of chronic obstructive disease of the airways and asthma **represents a departure from the specification and the claims as originally filed**.

Applicant's amendment on 08/30/2004 does not point to the specification for support for the newly added claim limitations. The specification and the claims as originally filed do not provide a clear support of the claim amendments.

The word 'phospho-antigen' is mentioned in the 62-page specification 2 times and isoprenylpyrophospate was listed in the specification one time as an example of a 'phospho-antigen.' The specification does not contemplate any of the newly added claims, 36-53. Rather both a phospho-antigen and isoprenylpyrophosphate are listed in the specification on page 31,

lines 21-23 "for activation of gamma delta T cells." The claimed method was never contemplated using any phosphoantigen, nor using isoprenylpyrophosphate in particular.

7. Claims 36-53 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for : a method to reduce airway hyperresponsiveness in a mammal, consisting essentially of increasing gamma delta T cell action in a mammal that has, or is at risk of developing, a respiratory condition associated with airway hyperresponsiveness by administering TNF-alpha to the lung tissue of said mammal wherein administration of said TNF-alpha reduces airway hyperresponsiveness in said mammal; wherein said TNF-alpha is administered so that gamma delta T cells in the lung tissue of said mammal increases; wherein said TNF-alpha is administered so that gamma delta T cells in said mammal are activated; wherein said TNF-alpha is targeted to gamma delta T cells in the lung tissue of said mammal; wherein said TNF-alpha is targeted to gamma delta T cells having T cell receptor selected from the group consisting of a murine TCR comprising Vgamma4 and a human TCR comprising Vgamma1; wherein said TNF-alpha is administered by a route selected from the group consisting of inhaled, intratracheal and nasal routes; wherein said TNF-alpha is administered to said mammal in an amount effective to reduce airway hyperresponsiveness in said mammal as compared to prior to administration of said TNF-alpha; wherein said TNF-alpha is administered with a pharmaceutically acceptable excipient; wherein said TNF-alpha is administered within between 1 hour and 6 days of an initial diagnosis of airway hyperresponsiveness in said mammal; wherein said TNF-alpha is administered within less than about 72 hours of an initial diagnosis of airway hyperresponsiveness in said mammal; wherein said TNF-alpha is

administered prior to development of airway hyperresponsiveness in said mammal; wherein increasing gamma delta T cell action by administration of said TNF-alpha decreases airway methacholine responsiveness in said mammal; wherein increasing gamma delta T cell action by administration of said TNF-alpha reduces airway hyperresponsiveness of said mammal such that the FEV1 value of said mammal is improved by at least about 5%; wherein increasing gamma delta T cell action by administration of said TNF-alpha improves said mammal's $PC_{20methacholine}$ FEVt value obtained before increasing gamma delta T cell action when the mammal is provoked with a first concentration of methacholine is substantially the same as the $PC_{20methacholine}$ FEVt value obtained after increasing gamma delta T cell action when the mammal is provoked with double the amount of the first concentration of methacholine; wherein said first concentration of methacholine is between about 0.01 mg/ml and about 8 mg/ml; wherein said airway hyperresponsiveness is associated with a disease selected from the group consisting of chronic obstructive disease of the airways and asthma; does not reasonably provide **enablement** for a method to reduce airway hyperresponsiveness in a mammal, comprising increasing gamma delta T cell action in a mammal that has, or is at risk of developing, a respiratory condition associated with airway hyperresponsiveness by administering **a phosphoantigen** to said mammal, wherein administration of said **phosphoantigen** reduces airway hyperresponsiveness in said mammal of claim 36; wherein the **phosphoantigen** comprises **isoprenylpyrophosphate (IPP)** of claim 37; wherein said **pyrophosphate** is administered so that gamma delta T cells in the lung tissue of said mammal increases of claim 38; wherein said **phosphoantigen** is administered so that gamma delta T cells in said mammal are activated of claim 39; wherein said **phosphoantigen** is targeted to gamma delta T cells in the lung tissue of said mammal of claim 40; wherein said

phosphoantigen is targeted to gamma delta T cells having T cell receptor selected from the group consisting of a murine TCR comprising Vgamma4 and a human TCR comprising Vgamma1 of claim 41; wherein said **phosphoantigen** is administered by a route selected from the group consisting of inhaled, intratracheal and nasal routes of claim 42; wherein said **phosphoantigen** is administered to said mammal in an amount effecting to reduce airway hyperresponsiveness in said mammal as compared to prior to administration of said phosphoantigen of claim 43; wherein said **phosphoantigen** is administered with a pharmaceutically acceptable excipient of claim 44; wherein said **phosphoantigen** is administered within between 1 hour and 6 days of an initial diagnosis of airway hyperresponsiveness in said mammal of claim 45; wherein said **phosphoantigen** is administered within less than about 72 hours of an initial diagnosis of airway hyperresponsiveness in said mammal of claim 46; wherein said **phosphoantigen** is administered prior to development of airway hyperresponsiveness in said mammal; wherein increasing gamma delta T cell action by administration of said **phosphoantigen** decreases airway methacholine responsiveness in said mammal of claim 48; wherein increasing gamma delta T cell action by administration of said **phosphoantigen** reduces airway hyperresponsiveness of said mammal such that the FEV1 value of said mammal is improved by at least about 5% of claim 49; wherein increasing gamma delta T cell action by administration of said **phosphoantigen** improves said mammal's $PC_{20methacholine}$ FEVt value obtained before increasing gamma delta T cell action when the mammal is provoked with a first concentration of methacholine is substantially the same as the $PC_{20methacholine}$ FEVt value obtained after increasing gamma delta T cell action when the mammal is provoked with double the amount of the first concentration of methacholine of claim 50; wherein said first

concentration of methacholine is between about 0.01 mg/ml and about 8 mg/ml; wherein said airway hyperresponsiveness is associated with a disease selected from the group consisting of chronic obstructive disease of the airways and asthma

The specification disclosure does not enable one skilled in the art to practice the invention without an undue amount of experimentation.

The method currently recited in the claims is not supported by disclosure or examples in the specification. There is no data in the specification to support the claimed invention, nor is the method in whole or in part disclosed using a phosphoantigen or IPP.

The recited method of reducing airway inflammation in any mammal by administering any phosphoantigen would not work. First, Cendron et al. (PTO-892, Reference V) describes phosphoantigens as being "mycobacterial non-peptide antigens" that require IL-2 to promote proliferation in vitro and in vivo. A strong initial Th1 response was seen in monkeys, but it was later followed up by an anergic/ hyporesponsive state where T cells are unresponsive to the antigen for up to 4 months after the initial administration (In particular, abstract, page 561, right column). The same response was shown in Sicard et al. (PTO-892, Reference V) where another phosphoantigen, BrHPP was used. The transient gamma delta T cell response returns to a baseline within 10-15 days and successive exposures to BrHPP along with requisite IL-2 induce less vigorous expansions of gamma delta T cells (In particular, paragraph spanning 5477-5478). The gamma delta T cell depletion was long lasting, with a 12-week recovery period not being

sufficient to restore the initial level of response. Therefore, the prior art shows that gamma delta T cells do not exhibit sustained activation in response to phosphoantigens for any therapeutic benefit where increased and sustained levels of phosphoantigen specific gamma delta T cells are sought.

Reasonable correlation must exist between the scope of the claims and scope of the enablement set forth. In view on the quantity of experimentation necessary the limited working examples, the nature of the invention, the state of the prior art, the unpredictability of the art and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

8. Claims 36-53 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Applicant is in possession of : a method to reduce airway hyperresponsiveness in a mammal, consisting essentially of increasing gamma delta T cell action in a mammal that has, or is at risk of developing, a respiratory condition associated with airway hyperresponsiveness by administering TNF-alpha to the lung tissue of said mammal wherein administration of said TNF-alpha reduces airway hyperresponsiveness in said mammal; wherein said TNF-alpha is administered so that gamma delta T cells in the lung tissue of said mammal increases; wherein said TNF-alpha is administered so that gamma delta T cells in said mammal are activated;

wherein said TNF-alpha is targeted to gamma delta T cells in the lung tissue of said mammal; wherein said TNF-alpha is targeted to gamma delta T cells having T cell receptor selected from the group consisting of a murine TCR comprising Vgamma4 and a human TCR comprising Vgamma1; wherein said TNF-alpha is administered by a route selected from the group consisting of inhaled, intratracheal and nasal routes; wherein said TNF-alpha is administered to said mammal in an amount effective to reduce airway hyperresponsiveness in said mammal as compared to prior to administration of said TNF-alpha; wherein said TNF-alpha is administered with a pharmaceutically acceptable excipient; wherein said TNF-alpha is administered within between 1 hour and 6 days of an initial diagnosis of airway hyperresponsiveness in said mammal; wherein said TNF-alpha is administered within less than about 72 hours of an initial diagnosis of airway hyperresponsiveness in said mammal; wherein said TNF-alpha is administered prior to development of airway hyperresponsiveness in said mammal; wherein increasing gamma delta T cell action by administration of said TNF-alpha decreases airway methacholine responsiveness in said mammal; wherein increasing gamma delta T cell action by administration of said TNF-alpha reduces airway hyperresponsiveness of said mammal such that the FEV1 value of said mammal is improved by at least about 5%; wherein increasing gamma delta T cell action by administration of said TNF-alpha improves said mammal's $PC_{20methacholine}$ FEVt value obtained before increasing gamma delta T cell action when the mammal is provoked with a first concentration of methacholine is substantially the same as the $PC_{20methacholine}$ FEVt value obtained after increasing gamma delta T cell action when the mammal is provoked with double the amount of the first concentration of methacholine; wherein said first concentration of methacholine is between about 0.01 mg/ml and about 8 mg/ml; wherein said airway

hyperresponsiveness is associated with a disease selected from the group consisting of chronic obstructive disease of the airways and asthma.

Applicant is not in possession of :a method to reduce airway hyperresponsiveness in a mammal, comprising increasing gamma delta T cell action in a mammal that has, or is at risk of developing, a respiratory condition associated with airway hyperresponsiveness by administering **a phosphoantigen** to said mammal, wherein administration of said **phosphoantigen** reduces airway hyperresponsiveness in said mammal of claim 36; wherein the **phosphoantigen** comprises **isoprenylpyrophosphate (IPP)** of claim 37; wherein said **pyrophosphate** is administered so that gamma delta T cells in the lung tissue of said mammal increases of claim 38; wherein said **phosphoantigen** is administered so that gamma delta T cells in said mammal are activated of claim 39; wherein said **phosphoantigen** is targeted to gamma delta T cells in the lung tissue of said mammal of claim 40; wherein said **phosphoantigen** is targeted to gamma delta T cells having T cell receptor selected from the group consisting of a murine TCR comprising Vgamma4 and a human TCR comprising Vgamma1 of claim 41; wherein said **phosphoantigen** is administered by a route selected from the group consisting of inhaled, intratracheal and nasal routes of claim 42; wherein said **phosphoantigen** is administered to said mammal in an amount effecting to reduce airway hyperresponsiveness in said mammal as compared to prior to administration of said phosphoantigen of claim 43; wherein said **phosphoantigen** is administered with a pharmaceutically acceptable excipient of claim 44; wherein said **phosphoantigen** is administered within between 1 hour and 6 days of an initial diagnosis of airway hyperresponsiveness in said mammal of claim 45; wherein said

phosphoantigen is administered within less than about 72 hours of an initial diagnosis of airway hyperresponsiveness in said mammal of claim 46; wherein said **phosphoantigen** is administered prior to development of airway hyperresponsiveness in said mammal; wherein increasing gamma delta T cell action by administration of said **phosphoantigen** decreases airway methacholine responsiveness in said mammal of claim 48; wherein increasing gamma delta T cell action by administration of said **phosphoantigen** reduces airway hyperresponsiveness of said mammal such that the FEV1 value of said mammal is improved by at least about 5% of claim 49; wherein increasing gamma delta T cell action by administration of said **phosphoantigen** improves said mammal's $PC_{20methacholine}$ FEVt value obtained before increasing gamma delta T cell action when the mammal is provoked with a first concentration of methacholine is substantially the same as the $PC_{20methacholine}$ FEVt value obtained after increasing gamma delta T cell action when the mammal is provoked with double the amount of the first concentrration of methacholine of claim 50; wherein said first concentration of methacholine is between about 0.01 mg/ml and about 8 mg/ml; wherein said airway hyperresponsiveness is associated with a disease selected from the group consisting of chronic obstructive disease of the airways and asthma.

The specification does not describe the word 'phosphoantigen,' but rather it describes the word 'phospho-antigen.' The genus term 'phosphoantigen' describes many non-peptide compounds, including as all yet undiscovered phosphoantigens. There is no support in the specification for any species of phosphoantigen other than isoprenylpyrophosphate (IPP). It is noted that throughout the literature 'IPP' stands for another molecule, mainly isopentenyl-pyrophosphate, so it is unclear to the Examiner whether the recited compound is actually useful

in the claimed invention, given the lack of literature on the compound. Neither the exemplary embodiments nor the specification's general method appears to describe structural features, in structural terms, that are common to the genus. That is, the specification provides neither a representative number of species (phosphoantigens) to describe the claimed genus, nor does it provide a description of structural features that are common to species (phosphoantigens). As discussed above, the specification provides no structural description of phosphoantigens other than IPP, specifically exemplified; in essence, the specification simply directs those skilled in the art to go figure out for themselves what the claimed **phosphoantigen** looks like. The specification's disclosure is inadequate to describe the claimed genus of all phosphoantigens for use in the claimed method.

Applicant has disclosed only the phosphoantigen species 'isoprenylpyrophosphate', but has provided no description of using the compound in the claimed method. The skilled artisan cannot envision all the contemplated phosphoantigen possibilities recited in the instant claims. Consequently, conception cannot be achieved until a representative description of the structural and functional properties of the claimed invention has occurred, regardless of the complexity or simplicity of the method.

Adequate written description requires more than a mere statement that it is part of the invention. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC1993). The Guidelines for the Examination of Patent Application Under the 35 U.S.C.112, ¶ 1"Written Description"

Requirement make clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 20001, see especially page 1106 3rd column).

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

9. No claim is allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nora M. Rooney whose telephone number is (571) 272-9937. The examiner can normally be reached Monday through Friday from 8:30 am to 5:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

April 25, 2007

Nora M. Rooney, M.S., J.D.

Patent Examiner

Technology Center 1600

Maher M. Haddad

MAHER M. HADDAD
PRIMARY EXAMINER